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RESEARCH ARTICLE

# BONE MARROW MESENCHYMAL STEM CELLS ALLEVIATE STREPTOZOTOCIN-INDUCED HEART DAMAGE IN RATS: A MICROSCOPIC STUDY

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## ABSTRACT

One of the most prevalent illnesses worldwide is the cardio-vascular diseases. It is imperative to discover an effective natural preventive agent against myocardial injury. Changes to the amplitude and time duration of cardiac muscle contraction are among the contractility abnormalities that have been noticed in the rat heart that have diabetes produced by streptozotocin (STZ). In the current study, the possibility of bone marrow mesenchymal stem cells (BM-MSCs) to shield rats' hearts against STZ-induced cardiac injury was investigated. Three equal groups of rats were allotted: (i) the control group received a saline solution (0.9%); (ii) the STZ group received a single intraperitoneal (IP) dose of 45 mg STZ/kg of body weight; (iii) the STZ/MSCs group received one IP dose of 45 mg STZ/kg body weight and an intravenous (IV) single dose of $3\times10^6$ MSCs/rat after 8 days to induce cardiac damage. After four weeks of receiving BM-MSCs, all of the experimental rats groups were euthanized. The histology and ultrastructure of the heart were studied. Widely-spaced cardiac muscle fibres, necrotic myocytes with profoundly eosinophilic cytoplasm, and intercellular mononuclear cellular infiltration were the hall-marks of the marked pathological lesion that STZ caused. However, administration of BM-MSCs effectively mitigated the severe cardiac effects of STZ, and restored the histological and ultrastructural architecture of rats' hearts. In conclusion, the present study demonstrated the protective potentials of BM-MSCs for reducing heart fibrosis in rats, which may be used as an adjuvant therapy for heart fibrosis.

## INTRODUCTION

Myocardial infarction (MI) is one of the most prevalent causes of death in both industrialized and developing countries for both men and women. Despite scientific and medical progress, MI continues to rank among the most prevalent and deadly health issues in the contemporary world[1]. An imbalance in both the supply and need of coronary blood causes myocardial ischemia injury and destroys the cardiomyocytes, which is the hallmark of MI[2]. Oxidative stress brought on by the secretion of reactive oxygen species (ROS) during ischemic damage is a key element in the emergence of MI. When ischemia persists for a long

time at a dangerous level in MI, myocardial cell harm and/or death may result[3].

The antibiotic/antitumor streptozotocin (STZ) was first derived from *Streptomyces achromogenes* in the late 1950s[4]. Since STZ was discovered to be specifically toxic to the beta cells of the pancreatic islets in the middle of the 1960s, it has been utilized to treat beta cell malignancy in humans, as well as in inducing animal models of diabetes. The Food and Drug Administration approved STZ's use as cancer treatment in July 1982[4]. In experimental mice, STZ causes diabetes mellitus by destroying the β-cells in the pancreas that produce insulin. Through the low affinity glucose transporter GLUT2, pancreatic beta cells preferentially accumulate the poisonous analogue STZ[4,5]. The breakdown products and free radicals produced by STZ initiate the toxic effector pathway, which leads to the destruction of pancreatic β-cells by DNA alkylation, mitochondrial system impairment, and inhibition of O-GlcNAcase[5].

The mesenchymal stem cells (MSCs) are stromal cells that exhibit multi-line age discrimination and the ability to self-renew[6]. They are able to be isolated from various tissues such as bone marrow, adipose tissue, and the umbilical cord. Because of their multipotent qualities, MSCs constitute a special option for clinical studies. Bone marrow MSCs (BM-MSCs) are the stem cells that reside in the milieu of the bone marrow[6]. The following are some of the advantages of BM-MSCs: simple collection, rapid multiplication, expansion *in vitro*, durable self-renewal capabilities *in vivo*, and lack of questionable ethical issues[7]. Cell-based therapy is a tempting alternative to conventional pharmaceutical treatments. BM-MSCs offer a viable source of stem cells in addition to cell therapy options because of their multi-lineage potential, anti-inflammatory qualities, capacity to elude the defences of the host, and relatively easy culture growth[8]. Since MSCs are distinct multipotent cells with potent immuno-modulatory capabilities, clinical trials using MSCs are presently being conducted at various stages for a range of pathologic illnesses, such as inflammatory bowel diseases, inflammatory airway diseases, and graft versus host disease[9]. In the current study, the curative properties of BM-MSCs against rats' cardiac damage caused by STZ were investigated.

## MATERIAL AND METHODS

### Chemicals and isolation/culturing the BM-MSCs

The STZ and most of the other used chemicals were purchased from (Sigma, CA, USA). The BM-MSCs were extracted from the tibiae and femurs by flushing them with Dulbecco's modified Eagle's medium supplemented with 10% foetal bovine serum[10]. The nucleated cells were separated using a density gradient Ficoll/Paque (Sigma), and they were subsequently suspended in a complete culture medium containing 1% penicillin-streptomycin. The cells were grown in 5% humidified $CO_2$ at 37°C. Following 80-90% confluence, the cultures were centrifuged, suspended in media supplemented with serum, and incubated in a Falcon 50 $cm^2$ culture flask. The trypsinization process took place for 5 minutes at 37°C using 0.25% trypsin and 1.0 mM EDTA. The cultures were then rinsed with phosphate buffer saline (Sigma).

### Experimental animals and design

Before the experiment started, male albino rats (*Rattus norvegicus*), weighing between 100 and 120 g, were given a week to get use to the lab environment. The animals were housed in conditions with a 12:12 light/dark cycle, between 23 and 25°C, with unrestricted access to food and water. The following protocol was followed for splitting thirty male albino rats uniformly and randomly into three distinct groups of ten rats each: the control group received intraperitoneal (IP) injection of 2.5 ml saline solution (0.9%); the STZ group received IP 45 mg STZ/kg body weight[11]; the STZ/MSCs group received IP 45 mg STZ/kg body weight and intravenous injection of

$3\times10^6$ BM-MSCs/rat after 8 days to induce cardiac damage according to Fikry *et al*. with some modifications[12]. Following a 4-week period of MSC implantation, all rats in each experimental group were euthanized with $CO_2$. The Women's College for Arts, Science, and Education at Ain Shams University has approved the animal experiments in compliance with ethical standards (approval number: 1332408001).

**Histological examination**

The heart ventricular samples from all groups were fixed in formalin and placed into paraffin, sectioned (5 µm thickness sections and 1.0 µm semi-thin sections), stained with haematoxylin and eosin and 1% toluidine blue and examined by a light microscope[13].

**Ultrastructure examination**

Other heart ventricular samples were divided into tiny, 1-mm-3 pieces, which were then instantly fixed in 2.5% glutaraldehyde for 24 to 48 hours. The samples were then post-fixed in a buffered solution containing 1.0% osmium tetroxide at 4°C for two hours, and then they were rinsed in phosphate buffer (pH 7.2) three to four times for 20 minutes each. The fixed specimens underwent two changes of propylene oxide clearing, were embedded in resin and dehydrated in increasing degrees of ethyl alcohol (30-100%). Using an ultramicrotome (Ultracut RMC MT6000, Leica Microsystems, Wetzlar, Germany), ultrathin sections (60-90 nm thick) were cut with a diamond knife, mounted on copper grids, and doubly dyed with lead citrate and uranyl acetate. A transmission electron microscope (JEOL, Akishima, Tokyo, Japan) operating at 60-70 kV was used to see and take pictures of the grids at Ain Shams University's Faculty of Science.

**Statistical analysis**

The scoring for histological heart injury has been done for five samples from each tested group[14]. Besides, semi-quantitative analysis was done for mitochondria in ultrathin sections (20 area/sample; 5 sample/group) using ImageJ software[15]. The statistical analysis was done using GraphPad Prism (version 5, CA, USA), where one-way analysis of variance with Bonferroni *post-hoc* test was used to compare among tested groups and $P\leq0.05$was considered significant.

## RESULTS

**BM-MSCs alleviated the histological changes in myocardium of STZ-treated rats**

The cardiac muscle fibres of the control group's left ventricle displayed normal histological structure when seen under a light microscope in haematoxylin/eosin-stained and toluidine blue-stained sections. It is composed of muscle fibres that branch and anastomose, with granular acidophilic sarcoplasm and central oval nuclei. The spaces between the muscle fibres were filled with blood vessels. The longitudinally cut fibres showed evidence of the intercalated discs (Figure 1A, B). Regular, closely spaced longitudinal cardiac muscle fibres with oval nuclei in the centre were also seen (Figure 1B). In contrast, the STZ group displayed focal regions of damage, myocyte cytolysis, and haemorrhage and extravagated blood (Figure 2A). Additionally, a heart segment from the same group was shown in Figure (2B), which displayed dilated gaps between transversal and longitudinal cardiac muscle fibres, isolated areas of myocyte cytolysis and death, and a large number of myocytes with profoundly eosinophilic cytoplasm. Slices likewise exhibited substantial degeneration of heart architecture, frequently spaced cardiac muscle fibres, necrotic myocytes with profoundly eosinophilic cytoplasm, and a noticeable infiltration of intercellular mononuclear cells (Figure 2C, D). The majority of the previously noted changes in the heart tissue had almost vanished in STZ/MSCs group; intercellular haemorrhage and tightly spaced, regular longitudinal cardiac muscle fibres with central oval nuclei were also seen (Figure 3).

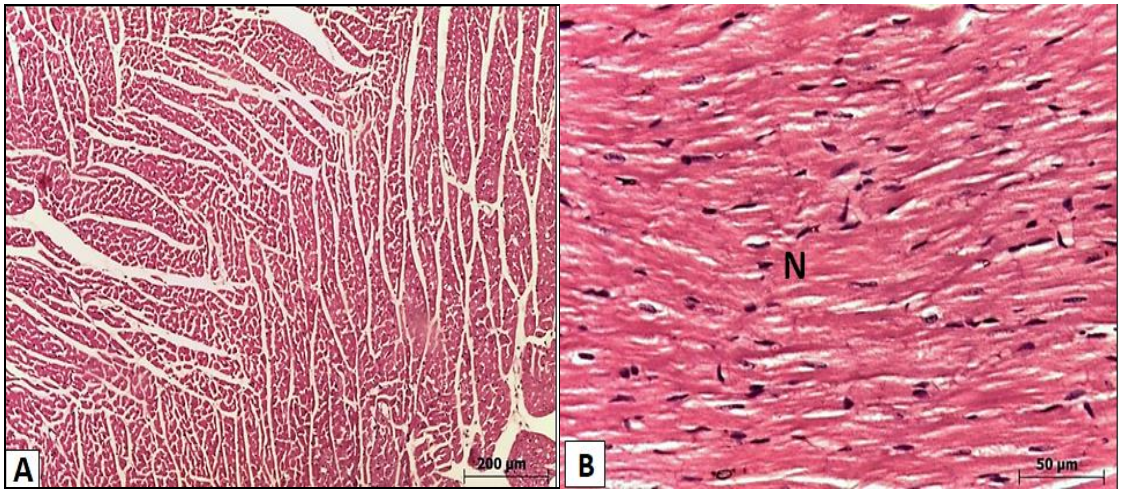


**Figure 1:** Photomicrographs of haematoxylin/eosin-stained sections of rat myocardium of the control group showing: **(A)** regular look of longitudinally-oriented cardiac muscle across muscle fibres (magnification: ×100, scale bar: 200 µm); **(B)** greater magnitude of Figure **(1A)**, scale bar: 50 µm, showing myocardial collections and central oval nuclei **(N)**.

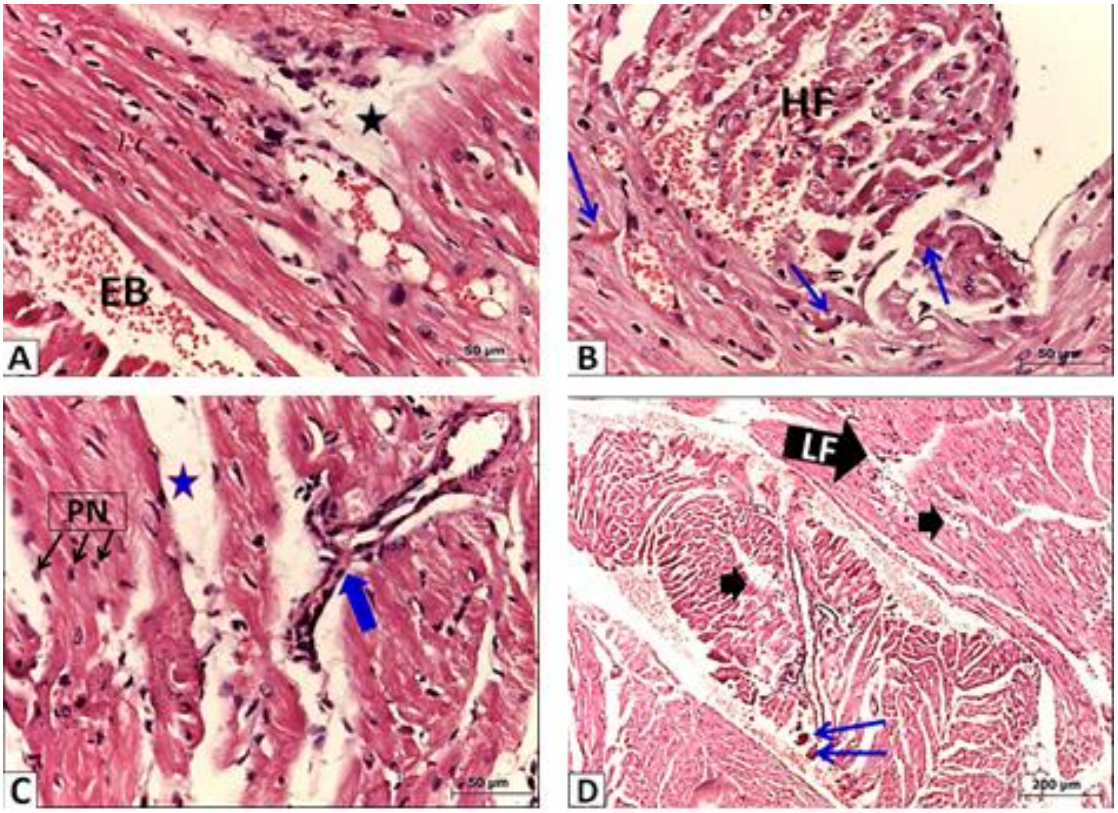


**Figure 2:** Photomicrographs of haematoxylin/eosin-stained sections of rat myocardium of the streptozotocin group showing: **(A)** areas of bleeding and extravasated blood (EB) and focal regions of devastation and cellular destruction of myocytes (star); **(B)** focal foci of myocyte cytolysis and dilated gaps between longitudinal and transversal cardiac muscle fibres, several myocytes with highly eosinophilic cytoplasm (arrows) and scattered haemorrhagic inflammation (HF); **(C)** necrotic myocytes with profoundly eosinophilic cytoplasm and widely dispersed cardiac muscle fibres (star), intercellular mononuclear cellular infiltration (thick arrow), and other pyknotic nuclei (PN); **(D)** focal loss of cross striations and focal areas of broken myofibres (arrowhead), and dilated blood capillary (arrows) with scattered inflammatory lymphocyte infiltration (magnification: ×400, scale bar: 50 µm).

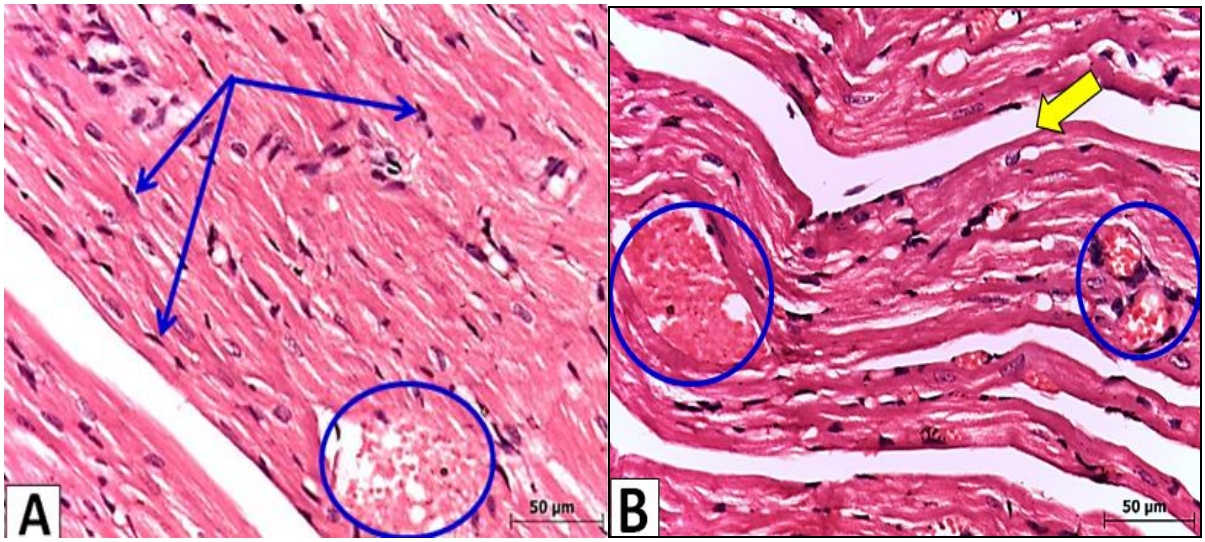


**Figure 3**: Photomicrographs of haematoxylin/eosin-stained sections of rat myocardium of the streptozotocin/mesenchymal stem cells group **(A and B)** showing relatively normal closely spaced longitudinal cardiac muscle fibres, with oval nuclei in the middle (blue arrows), take note of the intercellular haemorrhagic feature (rings), and separately myocardium (yellow arrow); magnification: ×400, scale bar: 50 µm.

The scoring for histological heart injury in the different groups of animals was shown in Figure (4). There was a significant elevation ($P \leq 0.05$) in the heart injury in STZ-treated group relative to the control group. While, administration of MSCs led to a significant decrease ($P \leq 0.05$) in the heart injury in STZ-treated group. There was a non-significant difference ($P > 0.5$) among the control and STZ/MSCs groups (Figure 4).

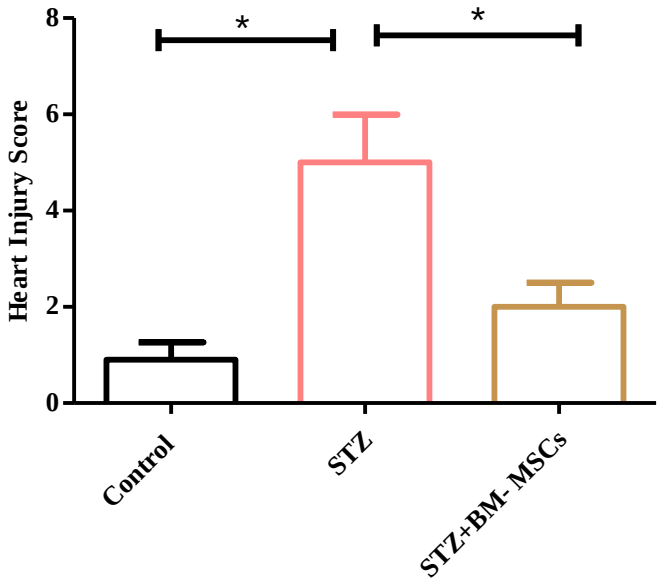


**Figure 4:** Heart injury score in various tested groups. Data are represented as mean± standard deviation, where *****refers to significant ($P \leq 0.05$).

Rat myocardium from the control group's semi-thin slices stained with toluidine blue revealed the typical appearance of transversely cut fibres; the central vesicular nucleus is visible (Figure 5A). Furthermore, widely split cardiac muscle fibres were also seen (Figure 5A). Rat myocardium from STZ group had marked myonecrosis, cardio-

myocyte lysis, as well as blood extravasation in between the injured muscle fibres (Figure 5B). Rat myocardium from STZ/MSCs displayed normal, closely spaced cardiac muscle fibres with oval nuclei in the middle; intercellular mononuclear cellular infiltration was existing (Figure 5C).

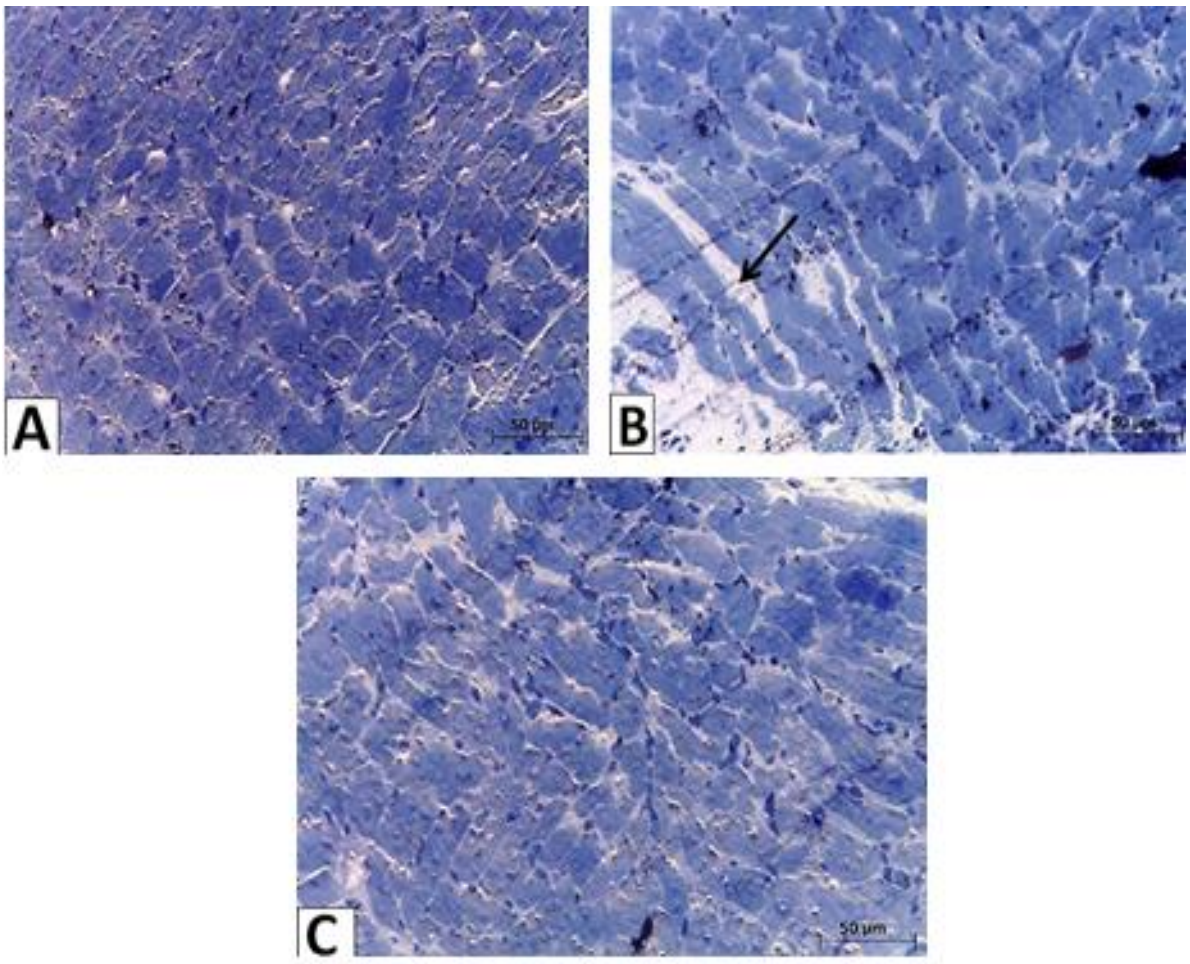


**Figure 5**: Photomicrographs of toluidine blue-stained sections of rat myocardium of the different groups: **(A)** the control group showing normal appearance of transversely cut fibres; **(B)** the streptozotocin group showing significant myonecrosis, lysis of the cardiomyocytes, and blood leaking into the spaces between the injured muscle fibres (the arrow indicating the widely separated heart muscle fibres); **(C**) the streptozotocin/mesenchymal stem cells group showing regular, closely spaced cardiac muscle fibres with oval nuclei in the centre (magnification: ×400, scale bar: 50 µm).

**BM-MSCs alleviated the ultrastructural changes in myocardium of STZ-treated rats**

The ultrastructural investigation of rats' myocardium in the control group revealed normal structure of the cardiac muscle fibres, which are joined side to side and end to end by intercalated discs (Figures 6). Sarcomere segments that repeat were found in the smaller myofibrils that make up these fibres. The mitochondria surround the euchromatic nucleus and are positioned parallel to and between the cardiac myofibrils. A set of dark lines, known as the Z line, denotes the separation of two sarcomeres. The area of the bright I band that contains actin thin filaments surrounds the Z line. Myosin thick filaments are found in the dark A band, which comes after the light I band. A softer area known as the H zone, which includes M line, is located within the A band. The thick filaments are connected to one another

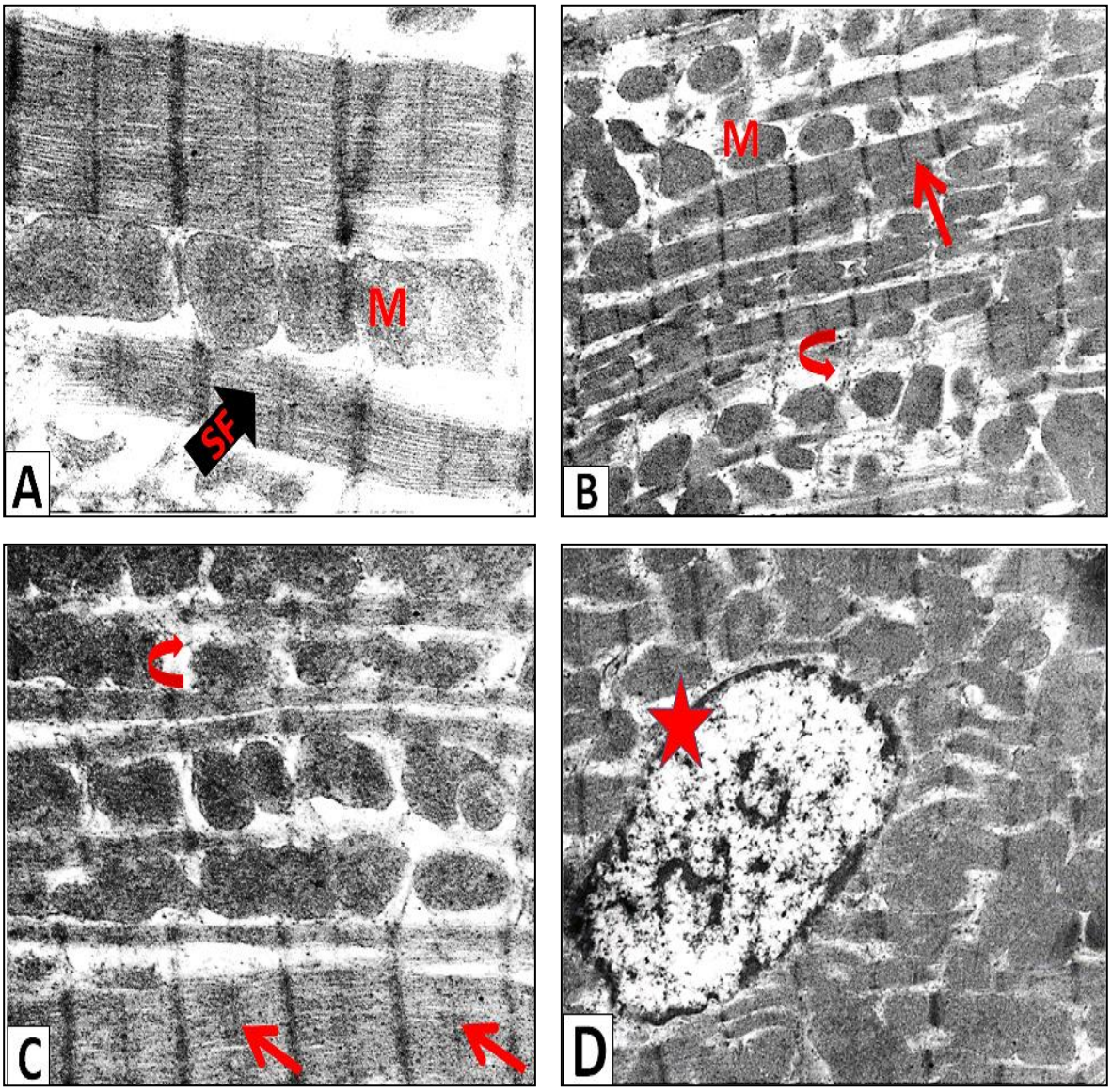


**Figure 6:** Transmission electron microscope photomicrographs of rat myocardium of the control group: **(A)** a coronary myocyte showing the sarcoplasm with regular rows of mitochondria (M), their tubular stuffed prominent cristae, and regular transverse striations of myofibrils (SF), magnification: ×25000; **(B)** cardiac myocytes showing normal myofilaments structured in sarcomeres (arrow) with variable sized mitochondria (M) organized in rows between myofibrils, and glycogen granules between the myofibrils (curved arrow), magnification: ×12000; **(C)** cardiac myocytes showing numerous glycogen granules (curved arrow) and normal myofilaments organized in sarcomeres (arrows), magnification: ×25000; **(D)** cardiac myocytes showing variably sized mitochondria, central oval nucleus with expanded chromatin (star), magnification: ×12000.

at the M line, which is located in the centre of the sarcomere. The centre oval elongated nuclei of the heart muscle fibres were visible. The nuclear membrane enclosed the nuclei, which exhibited a normal distribution of chromatin (Figure 6). The light microscopic findings were validated by the ultrastructural investigation of the left ventricular myocardium in STZ-treated rats, where abnormal nuclear envelope, perinucler region expansion, sarcoplasmic reticulum dilatation, and Z line interruption in focal locations were seen (Figure 7). There were also abnormally shaped, disorganized, and electron-dense

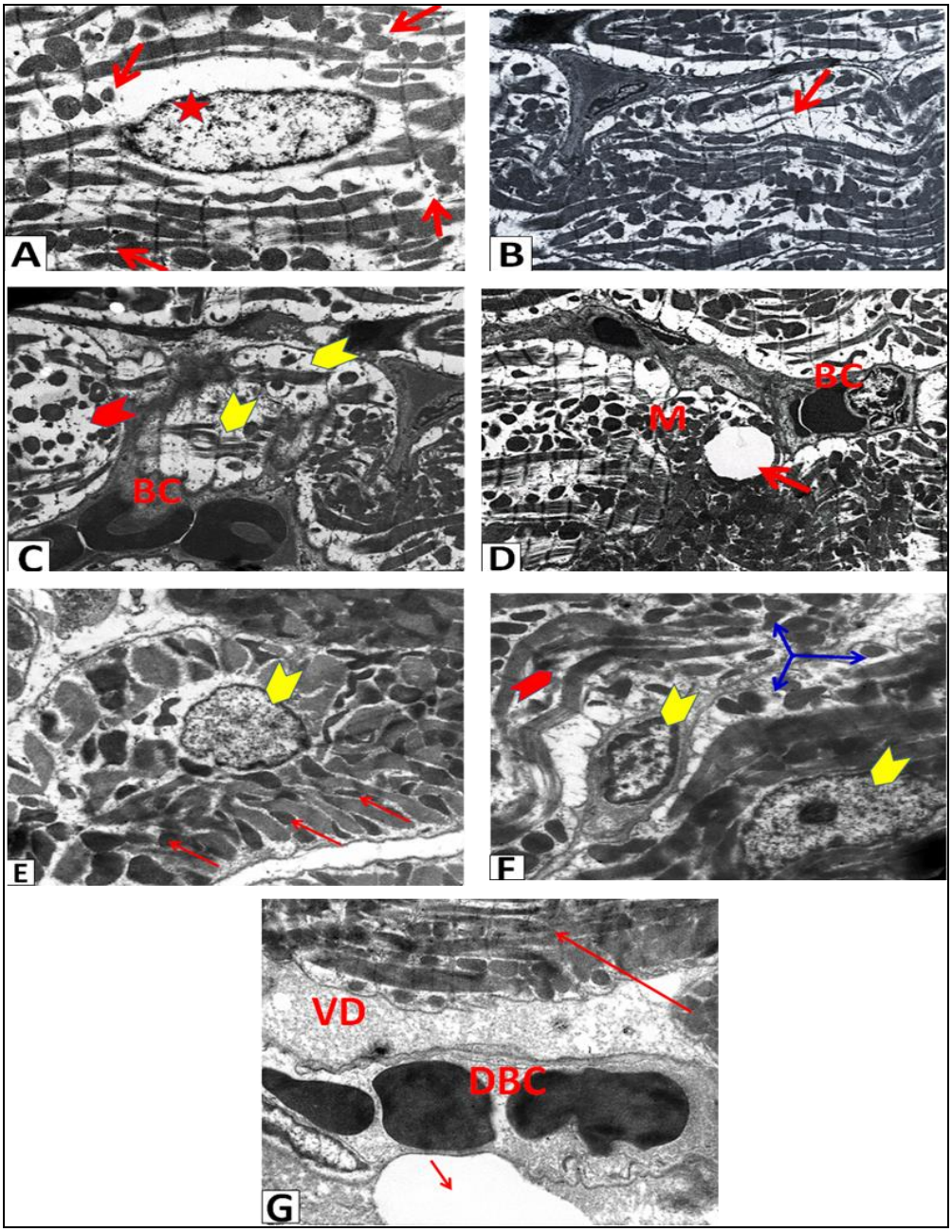


**Figure (7)**: Transmission electron microscope photomicrographs of rat myocardium of the streptozotocin group showing: **(A)** strangely shaped mitochondria oval nucleus (star), obviously destruction and lysis of myofibrils of the Z line, and mitochondria disarrangements division (arrows), magnification: ×6000; **(B)** completely collapsed and irregular myofibril structure (arrow), magnification: ×10000; **(C)** blood capillary congestion filled by red blood cell (BC), myofibril (yellow chevron), electron-dense mitochondria fragmentation (red chevron), and obstructed myofibrils, magnification: ×6000; **(D)** a large membrane-limited vacuole (red arrow) encircled by disorganized mitochondria (M) and congested blood capillary (BC), magnification: ×6000; **(E)** myofibril disintegration, electron-dense mitochondria (arrows) and distorted nucleus (yellow chevron), magnification: ×10000; **(F)** distorted irregular nuclei (yellow chevron) and myofibrillar destruction (red chevron) with irregularity mitochondria scattered (arrows), magnification: ×10000; **(G)** compressed myofibrils (long arrow) surrounded by vacuolar degenerative area (VD), as well as the presence of a big vacuole (short arrow) in the myocytes' sarcoplasm and dilated congestion blood capillary (DBC), magnification: ×10000.

mitochondria, as well as blood capillary congestion. The huge vacuoles found in the myocytes' sarcoplasm. The ordered parallel array becomes disorganized (as a result of myofibril disruption) dissociation, and lysis (Figures 7). The myofilaments and nuclei of rats treated with STZ/MSCs appeared relatively normal in the left ventricle (Figure 8), with minimal myofibrillar damage and modest sarcoplasmic vacuolation.

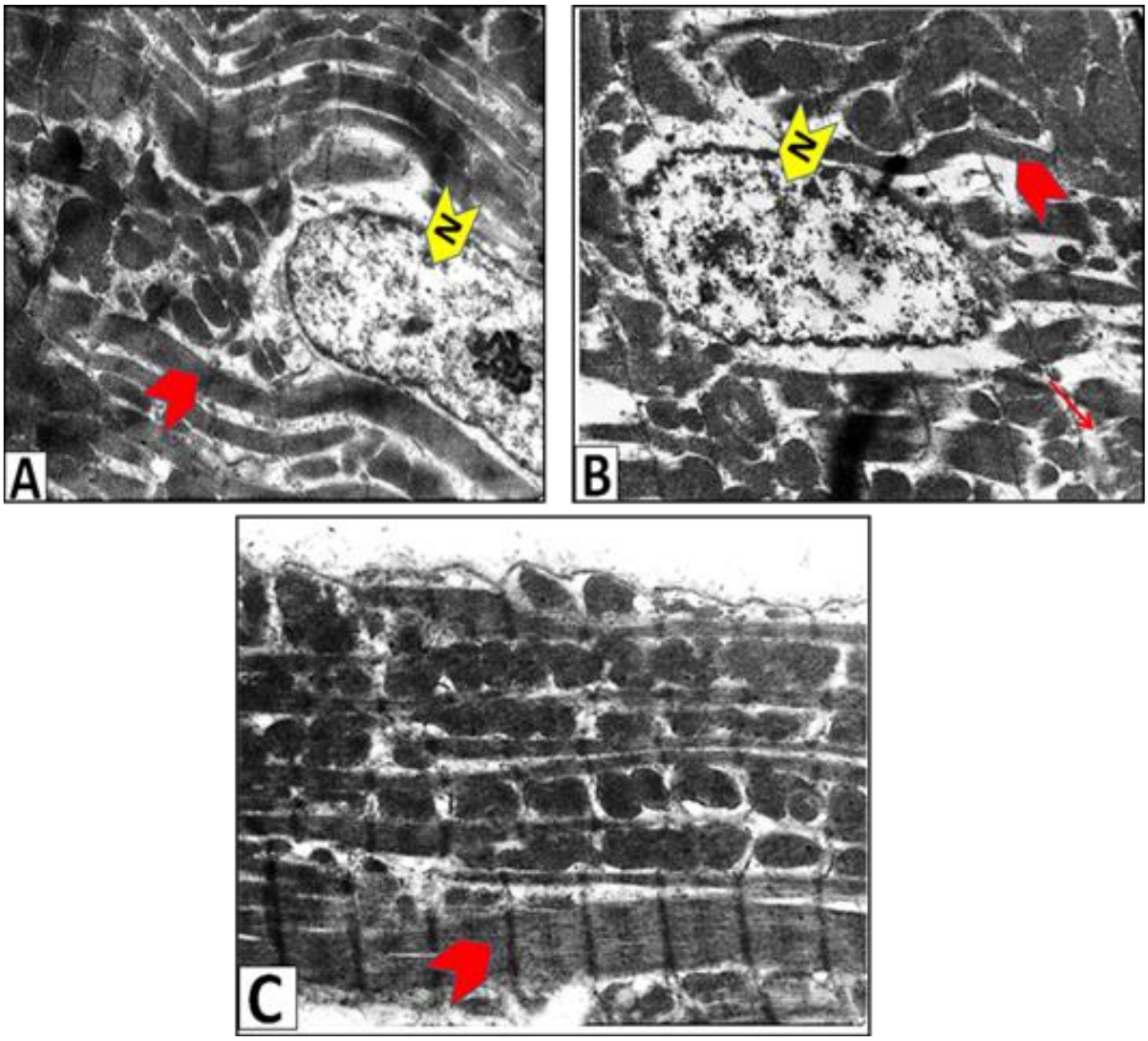


**Figure 8:** Transmission electron microscope photomicrographs of rat myocardium of the streptozotocin/mesenchymal stem cells group **(A-C)** showing relatively normal nucleus (N), regularly organized myofibrils (red chevron), and a rarely damage features of myofibrillar (arrow), magnification: ×12000.

A semi-quantitative analysis of mitochondria volume density in a random chosen microscopic regions in heart ultrathin sections in various groups of animals was shown in Figure (9). There was a significant rise ($P \leq 0.05$) in mitochondria volume density in STZ-treated group compared to the control group. While, administration of MSCs led to a significant reduction ($P \leq 0.05$) in STZ-treated group. There was a non-significant difference ($P > 0.5$) among the control and STZ/MSCs groups (Figure 9).

## DISCUSSION

The most common chronic illness, particularly in developing nations, is diabetes mellitus (DM). The severity of the disease's challenges is emphasized, and it is also

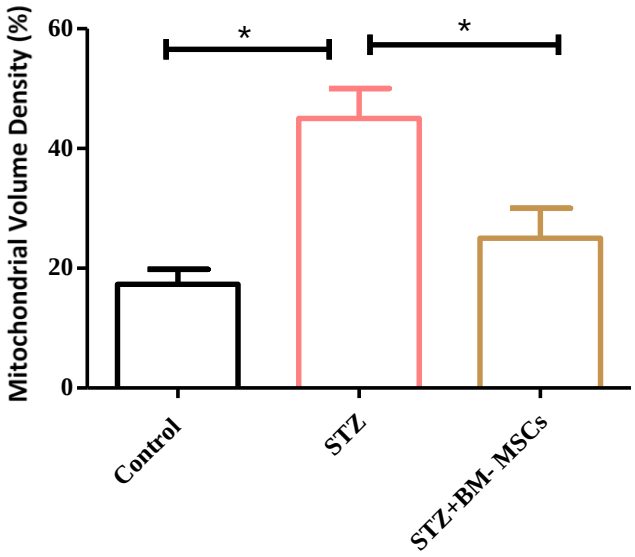


**Figure 9:** Mitochondria volume density (%) in various examined groups. Bars indicate the percentage of cytoplasm occupied by mitochondria in the perinuclear area ± standard deviation, where *****refers to significant ($P \leq 0.05$).

regarded as a public health issue in view of the ageing and expanding population, raised urbanisation, rising rates of over-weight, obesity and inactivity, as well as higher survival rates among DM patients[16]. Diabetes mellitus can be artificially induced by administration of STZ - a glucose moiety containing a highly reactive nitrosourea group derived from *Streptomyces griseus* - which destroying the pancreatic β-cells that produce insulin. STZ has been employed as a diabetogenic agent in experimental animals[17,18].

The current study highlighted the beneficial function of BM-MSCs towards STZ-induced cardiac damage in rats. In the current investigation, the administration of STZ to albino rats resulted in a number of histological alterations in their hearts. These included myocyte cytolysis, focal areas of damage, and regions of extravasated blood and bleeding. In addition, there are numerous myocytes with profoundly eosinophilic cytoplasm, isolated areas of myocyte death and cytolysis, and dilated gaps among longitudinal and transversal cardiac muscle fibres. There was a loss of heart architecture, a separation of the cardiac muscle fibres, necrotic myocytes with a cytoplasm that was highly eosinophilic, and an invasion of intercellular mononuclear cells. In the same line, Howarth *et al*.[19] reported changes to the frequency and time course of cardiac muscle contraction among the contractility defects found in the rat heart that have diabetes produced by STZ. Moreover, ventricular myocytes from diabetic rats showed longer times to peak and half-relaxation, decreased rates of contraction and relaxation, and decreased amplitude of contraction[20]. STZ has been shown to directly affect contractile function in isolated myocytes[21]. Research using *in vivo* biotelemetry has shown that heart rate decreases gradually and quickly following the administration of STZ and that insulin replacement can partially restore heart rate[19].

In the present work, the most frequent histological abnormalities in the myocardium after STZ injection that were seen included vacuolar degeneration, coagulative necrosis, infiltration of inflammatory cells, and blood leaking between the injured muscle fibres. Furthermore, the electron micrographs displayed the following: dilated sarcoplasmic reticulum, atypical mitochondria, myofibrillar lysis and separation, interrupted Z lines, and disarray of the ordered parallel myofibrillar array. Certain investigators also revealed that animals treated with STZ experienced rapid weight

loss due to the deleterious effects of STZ, including DNA alkylation, hyperglycaemia, and necrotic lesions[22,23].

There is a correlation between increased production of ROS and oxidative impairment of tissue components in STZ-induced diabetes, which is characterized by hyperglycaemia[24,25]. When STZ causes diabetic rats, ROS and reactive nitrogen species (RNS) such as superoxide radical ($O^{2\bullet-}$), hydroxyl radical (•HO), hydrogen peroxide ($H_2O_2$), and peroxynitrite ($ONOO^-$) are produced, leading to oxidative stress. The development of advanced glycation products, glucose auto-oxidation, protein glycation, and the polyol pathway, which produces free radicals, are the causes of oxidative damage in STZ-induced diabetic rats[24,25].

Many investigators claimed that MSCs originating from BM-SCs are self-renewing progenitor cells that can develop both *in vitro* and *in vivo* into osteoblasts, chondrocytes, astrocytes, neurons, skeletal muscle cells, and cardiomyocytes[26,27]. In the current investigation, it is evident that stem cells therapy might lessen the severe cardiotoxicity brought on by STZ, leading to a morphology that was somewhat comparable to the control group. Fikry *et al*.[12], also demonstrated that in a methotrexate-induced rat cardiac fibrosis model, either BM-MSCs or adipose-MSCs function as antioxidant, antiapoptotic, and antifibrotic agents. According to Liu *et al*.[28], delivering MSCs to the ischemic kidney improves renal function, speeds up the mitogenic response, and lowers cell apoptosis. Besides, MSCs can prevent renal tissue damage and the rise in inducible nitric oxide synthase expression brought on by hypoxia[29,30]. In conclusion, the findings reported in the present context indicated that BM-MSCs reduced heart fibrosis in STZ-induced rat model.

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This research study did not receive any funding.

**CONFLICT OF INTEREST**
There are no conflicts of interest

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# الخلايا الجذعية الميزنكيمية من نخاع العظم تخفف من تلف القلب الناتج عن المعاملة بالستربتوزوتوسين في الجِرذان: دراسة مجهرية

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تُعد أمراض القلب الوعائية من أكثر الأمراض انتشارًا في العالم. لا بد من اكتشاف عامل وقائي طبيعي فعال ضد إصابة عضلة القلب. تُعد التغييرات في السعة والمدة الزمنية لتقلص عضلة القلب من بين تشوهات الانقباض التي تم ملاحظتها في قلوب الجِرذان المصابة بداء السكري الناجم عن المعاملة بالستربتوزوتوسين. في الدراسة الحالية، تم التحقق من إمكانية الخلايا الجذعية الميزنكيمية من نخاع العظم في حماية قلوب الجِرذان ضد إصابة القلب الناجمة عن المعاملة بالستربتوزوتوسين. وتم تخصيص ثلاث مجموعات متساوية من الجِرذان: (i) تلقت المجموعة الضابطة محلول ملحي (0.9%)؛ (ii) تلقت مجموعة الستربتوزوتوسين جَرعة واحدة داخل الصفاق تبلغ 45 ملجم من الستربتوزوتوسين/كجم من وزن الجسم؛ (iii) تلقت مجموعة الستربتوزوتوسين مع الخلايا الجذعية الميزنكيمية جَرعة واحدة داخل الصفاق تبلغ 45 ملجم من الستربتوزوتوسين/كجم من وزن الجسم وجرعة واحدة في الوريد تبلغ $3\times10^6$ من الخلايا الجذعية الميزنكيمية/جِرذ بعد مدة 8 أيام للحث على تلف القلب. وبعد أربعة أسابيع من تلقي الخلايا الجذعية الميزنكيمية من نخاع العظم، تم تنفيذ الموت الرحيم لجميع جِرذان المجموعات التجريبية. وتمت دراسة الأنسجة والبنية التحتية للقلب. وكانت ألياف عضلة القلب المتباعدة على نطاق واسع، والخلايا العضلية النخرية ذات السيتوبلازم المحب بكثافة لصبغ اليوزين، والتسلل الخلوي أحادي النواة بين الخلايا هي السمات المميزة للأعراض النسيجية المرَضية التي سببها الستربتوزوتوسين. ومع ذلك، فإن حقن الخلايا الجذعية الميزنكيمية من نخاع العظم خفف بشكل فعال من التأثيرات القلبية الشديدة التي أحدثها الستربتوزوتوسين وأعادت البنية النسيجية/التحتية لقلوب الجِرذان. في الختام، أظهرت الدراسة الحالية الإمكانات الوقائية للخلايا الجذعية الميزنكيمية من نخاع العظم للحد من تليف القلب لدى الجِرذان، التي يمكن استخدامها كعلاج مساعد لتليف القلب.